REMARKS

Claims 40-50 were pending in this application. By this Amendment, Applicant has amended claim 40 according to the suggestion of the Examiner to whom this application has been assigned. Applicant maintains that the amended claim 40 is well supported by the specification. Applicant has amended claim 48 to correct a typographical error. Applicant has hereinabove cancelled claim 50 without prejudice to Applicants' right to pursue the subject matter in a future application. Upon entry of this Amendment, Claims 40-49 will be pending and under investigation. Applicant maintains that there is no issue of new matters and respectfully requests the entry of this Amendment.

Claim Rejections - 35 U.S.C. § 112

Claim 50 is rejected under 35 USC § 112, first paragraph as failing to comply with the written description requirement.

In response, but with conceding the correctness of the Examiners' position and to expedite the prosecution of this application, Applicant has cancelled claim 50 without prejudice to pursue Applicants' rights in the future to pursue a continuation or divisional application, thereby rendering the grounds of objection moot.

Claims 40-44 and 46-50 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In response, but without conceding the correctness of the Examiner's position and to expedite the prosecution of this application, Applicant has hereby amended claim 40 to eliminate the terms "derived" and "whereas". Applicant believes that the amended claim 40 is in full compliance with the requirements of § 112. Accordingly, Applicant respectfully requests the recommendation and withdrawal of this ground of rejection.

Claim Rejections - 35 U.S.C. § 103 (a)

Claims 40-50 are rejected under 35 USC as being unpatentable over Ohtomo, et al. and further in view of Queen, et al.

In response, Applicant's claimed invention recites a re-engineered, or framework (FR)-patched immunoglobulin containing a heavy or light or heavy and light chain variable regions sequences from a parent antibody, in which at least one of the compartmentalized framework sequences, defined as FR1, FR2, FR3 and FR4 are replaced, or patched by the corresponding compartmentalized framework sequences from the heavy or light or heavy and light chain immunoglobulin variable region of a different species, respectively, wherein said re-engineered immunoglobulin comprises compartmentalized framework sequences from at least two different sources of different immunoglobulin chains, wherein said different immunoglobulin chains can be sourced from different immunoglobulins of the same species, or from different immunoglobulins of different species, and such re-engineered immunoglobulin binds specifically to an antigen with affinity within 3-fold of that of the parent immunoglobulin with the proviso that not all the replaced FR1, FR2 and FR3 of the re-engineered immunoglobulin heavy chain are from the same

framework of a single immunoglobulin heavy chain; and not all the replaced FR1, FR2 and FR3 of the re-engineered immunoglobulin light chain are from the same framework of a single immunoglobulin light chain.

Ohtomo, et al. did not teach swapping FRs that are within the same V gene structures with one another, explicitly or implicitly. Ohtomo et al teach a "process", through the construction of a "hybrid" antibody in identifying the proper residues to be back-mutated in a classical "humanized" antibody. Ohtomo, et al. did not suggest the usability of the intermediary "process" as a form of a product. Rather, once they used the "process' and identified the "important residue" to be back mutated, they constructed the classical humanized (CDR-grafted) antibody as their final product. Moreover, Ohtomo did not teach the use of human FR1, FR2 and FR3 from different human sources as a way in making a re-engineered antibody with reduced immunogenicity. After reading the teaching of Ohtomo et al., one with ordinary skill in the art would be tempted to make a hybrid to help identify important residues to be mutated, and then move on to do humanization by the techniques of CDR-grafting, and if necessary, plus back mutation, still using the FR1, FR2 and FR3 from one single source. Without innovative hypotheses and undue experiments, one would not be sure if assorting FR1, FR2 and FR3 from different sources would upset the folding, expression, and VL/VH interactions of the reengineered antibody, leading to problems such as expression failure, misfolding, loss of immunoreactivity, etc.

Ohtomo, et al. did not use the "process" and the "hybrid" example to help make the selection of a different FR4 for the VH

desgin. Ohtomo et al did not explain the rationale for choosing a different FR4 for the construction of the humanized heavy chain. However, it was noted on p. 469 under the section titled: Construction of humanized ONS-M21 heavy chain, the author chose "FRs 1, 2 and 3 from human EU antibody, and FR4 from human ND antibody" and the structure was "designed" based on the "codon usage" present in antibody variable regions. The choice of a different FR4 appeared arbitrary and did not bear any relevance to the teaching of Ohtomo in their use of the hybrid (on the light chain variable region).

Again on p. 409, Ohtomo illustrated in Figure 2 that "the FR1, FR2, and FR3 sequences from human EU antibody (Cunningham et al., 1970) and the FR4 from human ND antibody (Kenten et al. 1982)", with no further elaboration. However, on p. 411 of Ohtomo's paper, under the section: Design and analysis of the humanized ONS-M21 heavy chain, in their design of the humanized VH sequence, Ohtomo et al compared sequence homology between the murine and human FR sequences, and identified "EU VH region of subgroup I to be highly homologous to the mouse ONS-M21 VH region (55.2% identity)". However, since "the human EU VH region contains unusual amino acid residues at positions 107, 108 and 110 in FR4", the "FR4 was chosen from human ND VH region", and the justification is that the ND VH region, like EU, "is also a member of subgroup I and contains more typical amino acid residues in its FR4".

Ohtomo, et al., were careful to point out that even though the FR4 was derived from a different antibody, yet they belong to the same group. Ohtomo, et al. were concerned that the choice of a different FR4 would be challenged by others, and thereby

making the above points to justify their choices. No suggestions whatsoever in the Ohtomo, et al. publication that FR1, FR2 and FR3 can be used to do homology search on an individual basis. The inference based on the use of a different FR4 for the construction of humanized VH sequence that FR1, FR2 and FR3 can be freely assorted is NOT obvious, because anyone with some basic knowledge in the genetic structure of immunoglobulin genes knows that FR4 resides in the J gene, and there are about 5 J genes available for human, whereas there are hundreds of V genes for the heavy and light chain immunoglobulin. It is obvious for those skilled in the art to contemplate mimicking the natural VJ or VDJ recombination by assorting J (FR4) sequences, but will find it inconceivable under normal scientific senses that sequences within the V gene (FR1, FR2, and FR3) can be freely assorted and result in a functional protein with reduced immunogenicity.

Therefore, the teachings by Ohtomo, et al. did NOT explicitly or implicitly suggest to or teach anyone skilled in the art and knowledge of humanization to extend such example to the free assortment of FR's within the same genetic structure of the V gene. The structure of the present invention is clearly different from that of Ohtomo, et al. In fact, anyone with some basic knowledge on molecular immunology will not venture into using free assortments of FR1, FR2 and FR3 because (1) such assortments are unprecedented and unusual; (2) the 3-D structure of the resulting protein might be distorted leading to expression, folding and/or functional problems. To say it is obvious to deduce the notion of free assortments of FR1, FR2, and FR3 within the same V gene structure without undue experimentation and hypothesizing based on one example of FR4

(JH gene) assortment (which occurs naturally and very predictable to be functionally feasible) is hardly convincing to those skilled in the arts of antibody engineering.

To support the fact that the example of FR4 assortment does not make free assortment of FR1, FR2 and FR3 obvious, we did a search in the publication on humanized antibody, and found numerous publications that used different FR4 region for humanization using the rationale of FR4 being within the J gene structure. None of them ventured into a free assortment of FR1, FR2 and FR3, as in the case of framework patching.

1. Shearman, C.W., Pollock, D., White, G., Hehir, K., Moore, G.P., Kanzy, E.J. and Kurrle, R. "Construction, expression and characterization of humanized antibodies directed against the human alpha/beta T cell receptor." J. Immunol. (1991) 147: 4366-4373.
   Remarks: VH EU | VL EU using the most homologous J regions (JH4 | JK4) **(Attached hereto as Exhibit A)**

2. Leung, S.O., Goldenberg, D.M., Dion, A.S., Pellegrini, M.C., Shevitz, J., Shih, L.B. and Hansen, H.J. 1995. Construction and characterization of a humanized, internalizing B-cell (CD22)-specific, leukemia/lymphoma antibody, LL2. Mol. Immunol. 32:1413-1427.
   Remarks: LL2 antibody humanized with VH NEWM/EU FR4 |VL REI. Again, NEWM FR1, 2, and 3 joined with EU FR4. **(Attached hereto as Exhibit B)**

3. Rosok, M.J., Yelton, D.E., Harris, L.J., Bajorath, J., Hellstrom, K-E., Hellstron, I., Cruz, G.A., Kristensson, K.,

Lin, H., Huse, W.D. and Glaser, S.M. "A combinatorial library strategy for the rapid humanization of anticarcinoma BR96 Fab" J. Biol. Chem. (1996) 271:22611-22618.

Remarks: Used germline FRs 1, 2, 3 VH HSIGDP51 SGIII/JH4 | VL HSIGVA23 SGII/Jk2. Again, free assortment of the J regions (JH4 and JK2). **(Attached hereto as Exhibit C)**

4. Hamilton, A.A., Manuel, D.M., Grundy, J.E., Turner, A.J., King, S.I., Adair, J.R., White, P., Carr, F.J. and Harris, W.J. "A humanized antibody against Human Cytomegalovirus (CMV) gpUL75 (gH) for prophylaxis or treatment of CMV infections" J. Infect. Diseases (1997) 176:59-68.

   Remarks: HCMV16 (SGIIA|kIII): VH NEWM or EU/FR4 NEWM | VL REI. They used EU FR1, 2, and 3 combined with the NEWM FR4. **(Attached hereto as Exhibit D)**

5. Riechmann, L., Clark, M., Waldmann, H. and Winter, G. "Reshaping human antibodies for therapy." Nature (1988) 332: 323-327.

   Remarks: YTH 34.5HL (IgG2a) Campath-1R: VH human NEWM, and VL human REI (with different human J region and mutations detailed in comments section). Again, they reshape using different FR4 using the J region recombination rationales.

The evidences provided above are overwhelming that while it is logical (matches with the natural VDJ/VJ recombination mechanism) and scientifically obvious to construct humanized antibody with different FR4 regions, as in the case of Ohtomo et al and the five other publications listed above, it is NOT obvious for those skilled in the art to venture into assorting the FRs within the V gene structure for purpose of humanization.

They are all constrained with the notion that FR1, FR2 and FR3 are inseparable and should be taken in its entirety, as they should be in the V gene.

The examiner to whom this application is assigned is making a quantum leap in assuming the teaching of Ohtomo, et al. could lead to the idea of framework patching. The article does not support such assumption; the science does not support such assumption; and the evidences provided have confirmed that the idea of framework patching described in this application is far from obvious, and requires substantial innovation and experimentation.

To compare the structure of the humanized heavy chain of Ohtomo, et al. (the V gene sequence joined to the J gene sequence) to a framework-patched sequence (the V gene disassembled and interrupted with different portions of FR1, FR2 and FR3 segments from different sequence) is like comparing a chimeric antibody (a recombined VDJ or VJ-gene joined to the human constant region gene sequence) to a CDR-grafted antibody (the recombined VDJ or VJ-gene interrupted with CDRs from a different source), the structural difference is obvious, especially when viewed from a genetic perspective.

Conclusion

In summary, Applicant believes that all grounds of rejections have been addressed and earnestly requests the Examiner to place this application in condition for allowance.

If a telephone interview would be of assistance in advancing the prosecution of the subject application, Applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fee, other than the FIVE HUNDRED AND TEN DOLLARS ($510.00), is deemed necessary in connection with the filing of this Communication. However, if any additional fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 50-1891. Conversely, authorization is also hereby given to credit the amount of any overpayment to Deposit Account No. 50-1891.

Respectfully submitted,

Albert Wai-Kit Chan

Albert Wai-Kit Chan
Registration No. 36,479
Attorney for Applicant(s)
Law Offices of
Albert Wai-Kit Chan, LLC
World Plaza, Suite 604
141-07 20th Avenue
Whitestone, New York 11357
Tel: (718) 799-1000
Fax: (718) 357-8615
E-mail: chank@kitchanlaw.com

I hereby certify that this paper is being deposited this date with the U.S. Postal Service with sufficient postage for first class mail addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Albert Wai-Kit Chan 12/7/05

Albert Wai-Kit Chan Date
Reg. No. 36,479